The Apnea Test: Rationale, Confounders, and Criticism
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What is This?
The Apnea Test: Rationale, Confounders, and Criticism

Ari R. Joffe, MD, FRCPC¹, Natalie R. Anton, MD, FRCPC¹, and Jonathan P. Duff, MD, FRCPC¹

Abstract
The apnea test is recommended for the diagnosis of brain death. There are several reasons this test should be reconsidered. Confounding factors for performing the test are vaguely and poorly specified. The following 2 confounders are usually present and not considered: potentially reversible high cervical spinal cord injury and central endocrine failure of adrenal and thyroid axes. There are case reports of breathing at a higher partial pressure of arterial carbon dioxide threshold and cases of recovery of breathing after brain death is diagnosed. The test is dangerous for an injured brain in the setting of high intracranial pressure. It can convert viable penumbral brain tissue to irreversibly nonfunctioning tissue via a transient increase in intracranial pressure and no-reflow phenomena. Hyperoxia during the apnea test can further suppress the function of medullary respiratory rhythm centers. Finally, the philosophical rationale for the need to show lack of spontaneous breathing in brain death is lacking.

Keywords
brain death, apnea, endocrine, carbon dioxide, respiration

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The apnea test is recommended in guidelines and for the diagnosis of brain death; however, this test has rarely been questioned in terms of its rationale, interpretation, or necessity in the diagnosis of brain death.¹⁻³ In this commentary, we question the empirical and philosophical rationale for doing the apnea test. Specifically, the literature usually neglects to mention the risks of doing an apnea test, the many potential confounders of interpretation of the test during severe brain injury, and the failure of the philosophical rationale to stand up to scrutiny. The apnea test should be reconsidered as a test to determine brain death in the setting of severe brain injury.

The Apnea Test
Several publications give guidance on the proper technique of performing an apnea test in suspected brain death.¹⁻⁴ Current guidelines recommend that the patient be preoxygenated, have a stable blood pressure, and have confounding conditions ruled out. During the apnea test, when the ventilator is not delivering any breaths, the patient is given oxygen via a catheter down the endotracheal tube or via continuous positive airway pressure by the ventilator or a manual bagger. The arterial carbon dioxide concentration is measured at baseline and should be about 40 mmHg. During the test, there is continuous observation of the patient for any respiratory effort. The arterial blood gas is measured intermittently, and when the arterial carbon-dioxide concentration rises to over 60 mmHg, and at least 20 mmHg above baseline, the test is stopped. If there are no observed respiratory efforts during the test, the apnea test demonstrates lack of a drive to breathe, and hence absence of function of the medullary respiratory centers. If there is hypoxia or hypotension during the testing, which makes the test invalid, the test is stopped and the hypoxia or hypotension is corrected.

The apnea test assesses for lower medullary function. If this function is lost, as shown by the apnea test, this demonstrates that the cascade of brain injury, cerebral edema, brain herniation, and injury of the entire brain, including the brainstem, has gone to completion.⁵ If the apnea test cannot be performed, an ancillary test is recommended to prove that there is a lack of brain blood flow.¹⁻³

The original studies of brain death did not require the apnea test as currently recommended because of the potential adverse effects.⁶⁻⁸ The Cerebral Survival Study, done by the advisors to the President’s Council from 1970 to 1972, defined apnea as a...

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lack of respiratory effort to override the ventilator for 15 minutes; the ventilator was not stopped or the ventilation rate even reduced. This definition of apnea was similar to other studies done before, which led to the acceptance of the concept of brain death. The current technique has never been tested as a criterion to define brain destruction or even irreversible lack of the drive to breathe.

### Potential Confounding Conditions

The apnea test should not be done if there are any confounding conditions that could affect its interpretation. Any condition that could alter the respiratory response to hypercarbia should be corrected prior to the apnea test, and if this cannot be done, an ancillary test is required.

#### Typical Confounding Conditions

Most clinicians are aware of the many potential confounding conditions that would make an apnea test not interpretable. The list includes: shock (hypotension); hypoxia; metabolic abnormalities (abnormalities of electrolytes, glucose, calcium, magnesium, phosphorus, renal and liver function, or ammonia); brainstem encephalitis; peripheral muscle or nerve dysfunction; endocrine abnormalities; hypothermia; and sedative or drug effects. One problem with this list is that each factor is vaguely or inconsistently specified (Table 1). The exact levels of hypotension, hypoxia, or metabolic values are not clear. The diagnosis of encephalitis, neuropathy, and myopathy is difficult, and neuropathy and/or polyneuropathy can be common during critical illness. The level of hypothermia suggested to confound interpretation of the test is inconsistent, with testing being recommended only after the temperature is at least 36.5°C in the United States, 35°C in Australia/New Zealand, and 34°C in Canada and the United Kingdom.

Medications are a common potential confounder. Which drugs to consider as confounding brain death is not clear, and new ones are reported intermittently as mimics of the state of brain death. Moreover, what dose and what exact level of the drug would confound the apnea test in the setting of severe brain injury is not clear and has never been studied. For example, opioids and benzodiazepines are commonly used in patients with severe brain injuries, and how long after therapeutic dosing (sometimes as prolonged infusions) and at what exact measured level would an apnea test be reliable is unknown. The ability to measure levels of these drugs is usually not available. The literature does not often discuss this problem, except in the setting of a barbiturate-induced coma, where many days are required before the drug effect can wear off.

The implications of the above are that physician judgment is required in interpreting possible confounding conditions. If the physician judges that a potential confounding condition is present, then this should be reversed prior to testing for brain death, or an ancillary test should be done in addition. How consistently different physicians may make the same subjective judgments has never been studied.

### Potential Confounding Conditions Not Typically Considered

Recently, cervical spinal cord injury and endocrine dysfunction, 2 potential confounding conditions to the apnea test, have unfortunately been described as very common in patients with severe brain injury who may be suspected to have brain death. High cervical spinal cord injury is a common consequence of any brain herniation event. A recent review summarized the many case reports of cervical spinal cord injury with acute quadriplegia and apnea during brain herniation because of various conditions including meningitis and trauma. It is concerning that in many of these cases the clinical findings were reversible over time. In the only 2 series of brain death that examined the spinal cord pathologically, 50% to 100% of cases had high cervical spinal cord damage secondary to the brain herniation event. In an animal model of brain death, the high cervical spinal cord was usually damaged. Spinal cord injury is a confounder to not just testing for movement to noxious stimulus and the cough reflex, but also testing for apnea. If apnea is because of cervical cord dysfunction, and not to medullary dysfunction, the apnea test result is confounded. This is a major problem because there is no validated test for high cervical cord injury. The best test for this injury would likely be magnetic resonance imaging (MRI); however, how sensitive and specific this test is for this purpose requires more study. In addition, obtaining MRI on patients with suspected brain death can be difficult, costly, impractical, and has its own hazards in a patient on vasoactive infusions. An ancillary test in all cases of suspected brain death would be another potential solution to the problem; however, brain blood flow testing with radionuclide imaging or single-photon emission computed tomography has not been validated in the setting of severe brain injury and its specificity in this setting is unclear.

A second major confounding condition is endocrine dysfunction. Although diabetes insipidus occurs in at least 50% of brain death cases, it is treated and therefore unlikely to confound testing for apnea. However, if the hypothalamus and/or pituitary gland are damaged during the brain injury and herniation, then central adrenal and thyroid deficiency should occur. Indeed, some guidelines recommend treating these deficiencies in brain death potential organ donors to improve organ function and hemodynamic stability. It is rarely mentioned that adrenal and thyroid deficiency states can cause coma and apnea. There are many reports of altered central response to carbon dioxide in hypothyroidism, with a raised threshold (higher than 60 mmHg) for central respiratory drive, even more exaggerated after exposure to any sedative. Since the pathophysiology of brain death includes usual injury to the pituitary, adrenal function and thyroid function should usually be deficient. This would require testing for, and the treatment of, any dysfunction prior to testing for brain death. This has not been recommended or done in any medical center to our knowledge.

A final confounder presents an interesting dilemma. It is known that high partial pressure of arterial carbon dioxide
decreases the level of consciousness by suppressing brain function.\textsuperscript{28} The effect of a high partial pressure of arterial carbon dioxide on a recently damaged brain is unknown. It can be speculated that a high partial pressure of arterial carbon dioxide can suppress the function of the respiratory center of the brain and increase the threshold for stimulation of breathing.\textsuperscript{29}

The Empirical Evidence for the Apnea Test

The threshold for diagnosing irreversible medullary respiratory centers’ loss of function has not been validated. Different guidelines suggest different thresholds of partial pressure of arterial carbon dioxide. For example, in Canada, the United States, and Australia/New Zealand the threshold is 60 mmHg, and in the United Kingdom it is 50 mmHg.\textsuperscript{1,2,10,11} In addition, the temperature at which an apnea test is allowed is different in Canada and the United Kingdom (34°C), Australia/New Zealand (35°C), and the United States (36.5°C).\textsuperscript{1,2,10,11} This is problematic given that there are case reports of 3 patients with brain death who had breathing efforts when the partial pressure of arterial carbon dioxide rose well above 60 mmHg.\textsuperscript{30-32} In addition, there are several case reports of patients (infants and adults) correctly diagnosed with brain death who later had a return of respiratory efforts.\textsuperscript{33} These reports include a 3-month-old patient who regained respirations over 30 days after having brain death correctly diagnosed.\textsuperscript{34}

It is usually claimed that if done correctly with preoxgenation, ongoing oxygenation during the test, and attention to hemodynamics, the apnea test can be done safely. Although reports give rates of complicating hypoxia and hypotension varying from 5% to 20%, it is generally felt that with constant monitoring, and aborting the test in event of an adverse effect, the apnea test is safe.\textsuperscript{4,35} Nevertheless, it is suggested to do the test only after all the other tests of brain death are fulfilled, presumably to avoid the potential complications in someone who is known not to have brain death.\textsuperscript{1,4,10,11} This reasoning may mask the fact that the deleterious effect of even transient hypoxia and/or hypotension on a recently injured and vulnerable brain is unclear. In the setting of brain injury, in general, avoiding hypoxia and hypotension are said to be the only proven interventions available in intensive care, given their consistent association with adverse outcomes.\textsuperscript{36}

Of potentially more concern is the effect of a high partial pressure of arterial carbon dioxide on a vulnerable brain in the setting of high intracranial pressure. It is recognized in neurointensive care that a high partial pressure of arterial carbon dioxide must be avoided, if possible, because of its known effect on raising intracranial pressure and therefore worsening ischemia to the brain and potentially contributing to herniation.\textsuperscript{28,29,37,38} The only widely accepted reason to induce hypocapnea in a brain injured patient is in the setting of suspected brain herniation to acutely reduce the intracranial pressure.\textsuperscript{38} In animal models of brain injury, once the intracranial pressure rises above systemic blood pressure, even transiently, there is often a no-reflow phenomenon with collapse of the cerebral vasculature that is often not reversible by lowering the intracranial pressure again.\textsuperscript{39,40} Given this information, it is logical to assert that an apnea test is potentially very dangerous to a recently injured brain that has high intracranial pressure.\textsuperscript{29} Indeed, it is reasonable to suggest that the apnea test itself can result in failing the apnea test, creating a self-fulfilling prophecy. During the apnea test, the rising partial pressure of arterial carbon dioxide causes an acute rise in intracranial pressure in any remaining perfused brain, and this in turn will worsen brain ischemia and complete any evolving herniation, reducing the function of any affected brain. Moreover, after the apnea test, these functions are likely not recoverable because of the no-reflow phenomenon.

An interesting slant on this concern has been raised by Coimbra.\textsuperscript{41} In the setting of brain ischemia it is widely recognized that there are irreversibly ischemic areas and penumbral areas where perfusion is low enough to cause a loss of clinical functions even though the tissue is viable if perfusion is restored.\textsuperscript{32} This is the rationale behind thrombolysis in the setting of ischemic brain and brainstem strokes.\textsuperscript{33} It is possible then that the apnea test can convert functioning brain to non-functioning penumbral brain (causing the failure of the apnea test), and can convert penumbral brain to irreversibly non-recoverable brain.\textsuperscript{41} Although this has not been proven empirically in the setting of suspected brain death, it is more concerning that it has not been refuted empirically in that
setting. Given the pathophysiologic soundness of the argument, it would seem a valid concern.

One reason the apnea test is done last in testing for brain death is that it is said to show that the herniation and brain injury have come to completion, affecting the lowermost part of the entire brain, the medulla. It is suggested that the typical sequence of brain death is progressive cerebral edema, intracranial hypertension, and herniation. This could be true; but it makes some facts present in many brain death patients difficult to explain. For example, there is electroencephalogram activity in 20%, brain blood flow in 5% to 40%, hypothalamic function in over 50%, and lack of pathologic destruction of brain and/or brainstem in over 40% of brain dead patients. It has been claimed that these are not relevant functions of the brain. Again, this could be true; however, it misses the point that if herniation occurs, then the brain blood flow should stop, brain functions should then cease, brain tissue should die, and brain edema should not resolve for a long time (there is no blood flow to reabsorb it). It is likely that a significant number of brain death patients have not had this typical sequence occur. These points are relevant to the apnea test for 2 reasons. First, they suggest that there could be viable penumbral brain tissue that could later perform a recognized clinical function, but the apnea test can seal its fate. Second, the reasoning behind doing the apnea test last, to confirm completion of the herniation process, could be flawed.

The Physiology of Respiration

A brief review of some respiratory physiology raises further concerns of the apnea test. There are 2 distinct rhythm generators in the medulla, the preBo¨tzinger complex composed of 600 neurons (in rats) responsible for inspiratory rhythm, and the retrotrapezoid nucleus/parafacial respiratory group responsible for expiratory rhythm. Transsection of the brainstem between these 2 centers results in continued respiratory rhythm at a slower frequency. Slowly developing lesions to the pre-Bo¨tzinger complex cause apneas to first occur during rapid eye movement sleep, later extending into nonrapid eye movement sleep, and finally into wakefulness. These lesions also cause markedly depressed responsiveness to partial pressure of arterial carbon dioxide levels, hypoxia, and hyperoxia, and marked sensitivity to anesthesia with apnea. In fact, with preBo¨tzinger complex lesions, hyperoxia results in marked depression of respiratory frequency, often with fatal apneas. More acute lesions to the preBo¨tzinger complex cause apnea during wakefulness. The preBo¨tzinger complex is also very sensitive to opioids, with quantal slowing of respiration when there is an intact retrotrapezoid nucleus/parafacial respiratory group, and fatal apneas when there is not, which can be reversed by giving naloxone. Chemosensation of pH (and hence of partial pressure of arterial carbon dioxide) is widespread in the brainstem, including the preBo¨tzinger complex, retrotrapezoid nucleus/parafacial respiratory group, and also nucleus tractus solitarius, locus ceruleus, midline medullary raphe, and the fastigial nucleus. Each of these contributes about 15% to 30% of the chemosensitivity to partial pressure of arterial carbon dioxide. These multiple sites, in medulla and pons, together maintain normal thresholds of sensitivity to partial pressure of arterial carbon dioxide. Sensitivity to partial pressure of arterial carbon dioxide is linear over a range extending up to 100 to 200 mmHg, with the slope of this partial pressure of arterial carbon dioxide/ventilation response curve having wide individual variation. The slope of the partial pressure of arterial carbon dioxide/ventilation response curve is also flattened by hyperoxia. This same functional anatomy of the control of respiration in the brainstem has been confirmed in a human functional MRI study. This information raises some concerns regarding the apnea test in determination of brain death. First, when only lower medullary function remains, the level of partial pressure of arterial carbon dioxide needed to stimulate breathing can be higher than 60 mmHg. Second, the amount of time required for opioid or anesthetic effects on respiratory rhythm to wear off are unknown. Third, the hyperoxia required to perform an apnea test without causing dangerous hypoxia can actually be what causes apnea to manifest, because of the suppression of function in the damaged preBo¨tzinger complex.

The above is likely an oversimplification of brainstem respiratory physiology. The core circuitry for eupneic (with 3 phases) breathing likely involves interactions among the Bo¨tzinger and preBo¨tzinger complexes in the rostral medulla, with modulatory brainstem inputs from the pontine respiratory group, retrotrapezoid nucleus/parafacial respiratory group, medullary raphe, and nucleus of the tractus solitarius. These hierarchical compartments are integrated in the intact brainstem, and the compartmental functions are revealed by serial brainstem damage. Eupneic breathing requires the entire system, including the pons. After pontomedullary transection, eupnea is transformed to a markedly altered 2-phase pattern. After transection in the rostral medulla, between the Bo¨tzinger and preBo¨tzinger complexes, only a gasping (slower, 1 phase) pattern occurs. Gaping is the one respiratory pattern that can be reproducibly obtained in medullary preparations. Gaping is not sensitive to hypercapnia; rather, gasping is recruited in severe hypoxia. Gaping is a respiratory effort to sustain life and is necessary for autoresuscitation from hypoxic coma and apnea in animals and humans. Acute lesions to the preBo¨tzinger complex can cause apnea, but eupnea often resumes over days as the brainstem respiratory network reconfigures. However, damage to a small, critical area of brainstem in the preBo¨tzinger complex, involving pacemaker neurons based on persistent sodium current, irreversibly eliminates gasping. This information on gasping raises another concern regarding the apnea test. The apnea test is used to determine lower medullary function, the innate drive to breathe, and completion of the cascade of brainstem injury; therefore, gasping is the function that should be assessed. Eupnea, stimulated by hypercapnia, is dependent on pontomedullary circuits, and altered 2-phase breathing stimulated by hypercapnia is dependent on the entire medulla (with chemosensory input from pons).
Gasing is dependent on only the medulla caudal to the Bötzinger complex, and is a sign of the organism attempting autoresuscitation.\textsuperscript{55-57,59} Hypercarbic hyperoxia, as in the apnea test, will not stimulate gasing even in an undamaged organism. Inducing severe hypoxia would be required to test for gasing, but is not acceptable given the harmful effects of hypoxia on a damaged brain.

The Philosophical Rationale For the Apnea Test

There are 3 main reasons offered to explain the importance of the apnea test to the concept of brain death. First, the brain is necessary for integration of the organism as a whole, and loss of this integration is what defines the concept of death itself.\textsuperscript{68,69} Accordingly, failure of the apnea test shows completion of the brain herniation event and complete loss of integration of the organism as a whole. If there are breathing efforts during the apnea test then the brain is still functioning and there is still integration of the organism as a whole. The problem is that both of these statements are false. Breathing during the apnea test can be just an attempt to respire, not even enough to sustain the organism. It is not integration, just an attempt at it.\textsuperscript{70} Furthermore, the brain now, even if it was a master organ before, “is no longer a master organ but merely a part of an organ that once was master . . . [suggesting the implausible idea that] the history of an organ is relevant to deciding if a characteristic of life is present.”\textsuperscript{70} In addition, there is no clear explanation as to why the presence of respiration must be spontaneous (ie, because of spontaneous brainstem activity).\textsuperscript{70,71}

Why is integrated functioning considered to be present when it is supported artificially in, for example, a diabetic who is artificially supplied with insulin, a patient with congenital central hypoventilation or a high cervical spine quadriplegic on a ventilator, or a patient with renal failure on dialysis? “Some argument would be needed for why artificiality in cause matters when ‘lower’ integrated functioning of the organism results but not when ‘higher’ integrated functioning results . . . It is not clear why completely replacing the component at the apex should be different from replacing a component somewhere else in the loop.”\textsuperscript{70} This suggests that the concept of death, the loss of integration of the organism as a whole, does not require that the integration be spontaneous.

Second, it is said that breathing shows that the “breath of life” is present.\textsuperscript{72} This is said to reflect a Judeo-Christian belief. The suggestion here is that the “conscious soul” has departed, and the “breath of life” is gone.\textsuperscript{72} This is a robust Cartesian dualism, and “is poetry, not physiology.”\textsuperscript{73} It is unclear how to translate this into a scientific or biological rationale for the apnea test and for brain death. Moreover, in clinical brain death with failure on the apnea test it is not necessarily true that the capacity for consciousness is lost, as the cerebral hemispheres can be relatively spared.\textsuperscript{72} There are several cases of brainstem death without cerebral death, including 1 series where this accounted for 3.6\% of brain death cases.\textsuperscript{74} More problematic for this rationale is that absent “breath of life” is present in many patients who are clearly not dead, for example, a high cervical spine quadriplegic patient dependent on the ventilator, a partially brainstem damaged patient dependent on a ventilator, patients with severe central neurogenic hypventilation, and others.\textsuperscript{74} Even adding unconsciousness does not solve the problem, because one would require an explanation for why both facts together are needed, and there are still patients considered alive that satisfy the requirement, such as a patient with permanent vegetative state and a cervical spine injury, or with permanent vegetative state and partial brainstem injury, both of whom still have gag, cough, corneal, pupillary, and other reflexes.

Third, the recent President’s Council offered a completely novel concept of death.\textsuperscript{75} An organism is no longer a whole when it cannot perform “the fundamental vital work of a living organism, the work of self-preservation, achieved through the organism’s need-driven commerce with the surrounding world.”\textsuperscript{75} According to this rationale, apnea shows there is not an unconscious innate “felt need” of the organism to exchange gases with the world. There are several problems with this argument. First, lack of the felt need to breathe occurs in brainstem injury without brain death, central neurogenic hypoventilation, Ondine’s curse (during sleep), and high cervical spinal cord injury. None of these patients, while on a ventilator, are dead. This suggests that nonspontaneous breathing counts, and indeed the President’s Council writes that “when the brainstem’s respiratory centers are incapacitated, the organism will not make or display any respiratory effort . . . If the death of the organism is to be prevented, some external ‘driver’ of the breathing process—a mechanical ventilator—must be used.”\textsuperscript{75,76} One cannot prevent death if it has already occurred.\textsuperscript{77} It is more likely that the felt need, as it applies to respiration, is for the actual exchange of gases with the environment, which continues during brain death while on a ventilator.\textsuperscript{78} Second, it is clear that breathing or consciousness is sufficient to prove life, and this means that lack of breathing and consciousness is necessary to prove death; however, this does not mean that lack of breathing and consciousness are sufficient to prove death.\textsuperscript{76} Many ongoing felt needs continue in brain death despite lack of breathing and consciousness, including the felt need to circulate blood to the organs to meet their needs, have gut peristalsis to eliminate solid wastes to the world, metabolize toxins from the outside world in the liver, excrete unneeded electrolytes and water into the environment, clot an incision to prevent losing blood into the world, fight infections to eliminate bacteria invading from the outside world, keep bacterial flora in the throat from invading the body from the outside world, etc.\textsuperscript{75,77} Perhaps if all of these [and likely more] felt needs are lost it would be sufficient to prove death. Third, by the new rationale, the following organisms are dead: the fetus; the irreversible vegetative state patient without the ability to breathe; the locked-in patient with consciousness, but complete paralysis, including the cranial nerves; the pure brainstem death patient; and the partially brainstem damaged comatose patient without the ability to breathe.\textsuperscript{71}
The rise in pCO2 can be expected to increase intracranial pressure, brainstem is unknown by apnea the "fundamental vital work of a living organism" are not confirmed integration of the organism; loss of the "breath of life"; and loss of the philosophical rationale for an apnea test is unclear: lack of medulla isolated from the pons.

Gasping is the respiratory pattern reproducibly obtained in the medulla is damaged Hyperoxia can cause fatal apneas when the preBötzinger complex in the medulla is damaged Hyperoxia is a routine part of the apnea test necessary to avoid dangerous hypoxia. This can result in apnea.

Hyperoxia during the apnea test prevents gasping. Inducing severe hypoxia to test for medullary gasping function would be unacceptable. Lack of apnea may not indicate ongoing integration, and apnea can coexist with ongoing integration. "Breath of life" is not a biological or scientific rationale and can be lost in patients who are alive. Apnea is not sufficient to prove death, and much "vital work" continues with apnea during brain death.

### Table 2. Potential Reasons, in Addition to Those in Table 1, to Abandon the Apnea Test When Diagnosing the State Called Brain Death

<table>
<thead>
<tr>
<th>Potential Problem</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spinal cord injury is often present</td>
<td>How to rule out this confounding condition is not known. These should be diagnosed and treated prior to brain death testing. How these should be tested for is unclear. There are cases of breathing occurring at a higher pCO2 than currently recommended for apnea testing. When only medullary function remains, it is expected that a much higher than normal pCO2 threshold will be present. This can convert ischemic penumbra tissue to irreversibly injured brain, which can result in apnea.</td>
</tr>
<tr>
<td>Pituitary/hypothalamic, adrenal, and thyroid insufficiency are often present</td>
<td>Hyperoxia is a routine part of the apnea test necessary to avoid dangerous hypoxia. This can result in apnea.</td>
</tr>
<tr>
<td>The level of pCO2 required to induce respiration in a damaged brainstem is unknown</td>
<td>Hyperoxia during the apnea test prevents gasping. Inducing severe hypoxia to test for medullary gasping function would be unacceptable. Lack of apnea may not indicate ongoing integration, and apnea can coexist with ongoing integration. &quot;Breath of life&quot; is not a biological or scientific rationale and can be lost in patients who are alive. Apnea is not sufficient to prove death, and much &quot;vital work&quot; continues with apnea during brain death.</td>
</tr>
</tbody>
</table>

Abbreviation: pCO2, partial pressure of arterial carbon dioxide.

### Implications

The criterion of brain death requires there be loss of all critical functions of the entire brain, including the brainstem. The dilemma faced is how to prove brain death (Table 2). To demonstrate lack of medullary function on the apnea test would require tests to prove lack of cervical spinal cord injury from the brain herniation, lack of (or treated) endocrine failure, and more clear and validated specification of other absent confounding conditions. This is a tall order. It is not clear that MRI is feasible, sensitive, or specific enough to rule out cervical cord injury. Assuming this can be done, the issue of the theoretical dangers of high partial pressure of arterial carbon dioxide during the apnea test still cannot be ignored. A test diagnosing the lack of brain viability, replacing the apnea test, would be highly desirable. This diagnostic test would require better validation of the current brain blood flow tests, as currently diffusible radionuclide brain blood flow testing specificity in severely brain injured patients has been demonstrated in only 41 patients, and single photon emission computed tomography blood flow testing specificity has been demonstrated in only 12 patients. Finally, what gold standard of brain death to use for comparison is problematic. For example, pathological brain necrosis is not seen on 5% to 40% of autopsies of brain death patients, even after over 24 hours of brain death. In the original studies, no clinical criteria for brain death had near perfect correlation with pathological brain necrosis.

A potential solution to the dilemma has been discussed in the literature. This solution argues that brain death is a neurologically devastating state with a very poor prognosis, but not death itself. Some argue that in this state of brain death the patient no longer has a future like ours, a future of value, or that what makes life worth living has been lost. According to this argument, with informed consent of patient or surrogate, organ donation prior to withdrawal of life support is reasonable. Although this could be active euthanasia, it has been argued that it is not morally different from withdrawal of life support at the end of life in other patients. When a ventilator is withdrawn with consent, the physician’s action (removal of the ventilator) causes the effect (patient’s death). Both removal of the ventilator and organ harvest are acts that cause the death, and the informed consent makes them justified acts.

According to this argument, it is a moral fiction that withdrawal of life support is simply allowing a natural death from the progression of the underlying disease. The question is now, “Is an apnea test required to allow the decision to donate organs?” Some tests would be required to determine the state of neurological devastation, and hence justify the decision to donate organs prior to death. Perhaps, with empirically validated longer periods of observation, empirical clarification of confounding factors, and empirical clarification of brain blood flow test specificity, an apnea test would not be necessary.

### Summary

The apnea test is usually done during examination for suspected brain death to prove lack of respiratory drive, which in turn shows lack of clinical medullary brain function. There are problems with this theory. First, confounding factors for performing the apnea test are vaguely and poorly specified (Table 1). More concerning is that 2 confounders are usually present and not tested for or considered: a potentially reversible high cervical spinal cord injury, and central endocrine failure of adrenal and thyroid axes. Second, the empirical evidence for the apnea test suggests that it is poorly validated, with case reports of breathing at a higher partial pressure of arterial
carbon dioxide threshold, and rare cases of recovery of breathing after brain death is diagnosed. Third, the apnea test is theoretically dangerous for an injured brain in the setting of high intracranial pressure. It can be expected to convert viable or penumbral brain tissue to irreversibly nonfunctioning tissue via transient increase in intracranial pressure and no-reflow phenomena. Although this is theoretical, it has a sound pathophysiological rationale, and has never been empirically refuted. Fourth, hyperoxia during the apnea test can further suppress the function of medullary respiratory rhythm centers. Fifth, the philosophical rationale for the need to show lack of spontaneous breathing in brain death is lacking. Like many of the arguments in the literature on brain death, once they are examined in detail, their initial persuasiveness is lost.\(^8\)

The implications for clinical practice are concerning (Table 2). First, some way to confirm the absence of a confounding condition would need to be empirically validated. Second, it would be desirable to avoid the apnea test altogether and to have an empirically validated test of brain and brainstem blood flow in patients with severe brain injury. Third, whether tests for the neurological devastation presumed in brain death (without an apnea test) would allow organ donation with consent, and a justified violation of the dead donor rule, requires open debate. These are weighty moral problems. Continuing to do the apnea test is not the solution in our view, as it ignores the very real concerns outlined in this review.

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**Contributors**

ARJ wrote the first draft of the manuscript. NRA and JPD critically reviewed and revised the manuscript. All authors contributed to the idea of the manuscript.

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